

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 547048060WO	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US03/33441	International filing date (<i>day/month/year</i>) 21 October 2003 (21.10.2003)	(Earliest) Priority Date (<i>day/month/year</i>) 21 October 2002 (21.10.2002)
Applicant UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☒ Unity of invention is lacking (See Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/33441

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/33441

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 21/04; C12Q 1/70

US CL : 435/6, 91.2; 536/23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 91.2; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE BIOSIS CAPLUS, Thymidylate synthase, cancer, polymorphism

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database NCBI, Accession Number AF279906, NCBI Entrez database nucleotide sequences, National Center for Biotechnology Information, National Library of Medicine, NIH (Bethesda, MD, USA), 14 February 2001, nucleotides 132-159.	1-10
X	US 6,087,486 A (WEINER et al.) 11 June 2000 (11.06.2000), SEQ ID NO:	1-10
X, P	KAZUYUKI et al. Identification and Functional Analysis of Single Nucleotide Polymorphism in the Tandem Repeat Sequence of Thymidylate Synthase Gene. Cancer Research. 15 September 2003, Vol. 63, pages 6004-6007, see entire document.	1-10
X, P	MANDOLA et al. A Novel Single Nucleotide Polymorphism within the 5' Repeat Polymorphism of the Thymidylate Synthase Gene Abolishes USF-1 Binding and Alters	1-10
---	Transcriptional Activity. Cancer Research. 01 June 2003, Vol. 62, pages 2898-2904, see entire document.	11-20
A		
Y	TRINH et al. Thymidylate synthase: A novel genetic determinant of plasma homocysteine and folate levels. Human Genetics. July 2002, Volume 111, pages 299-302, see entire document.	11-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

26 May 2004 (26.05.2004)

Date of mailing of the international search report

16 AUG 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer

Juliet Switzer

Telephone No. 703 308 0196

INTERNATIONAL SEARCH REPORT

PCT/US03/33441

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	IACOPETTA et al. A polymorphism in the enhancer region of the thymidylate synthase promoter influences the survival of colorectal cancer patients treated with 5-fluorouracil. British Journal of Cancer. 2000, Volume 85, No. 6, pages 827-830, see entire document.	11-20
Y	ULRICH et al. Searching Expressed Sequence Tag Databases: Discovery and Confirmation of a Common Polymorphism in the Thymidylate Synthase Gene. Eancer Epidemiology, Biomarkers & Prevention. December 2000, Vol. 9, pages 1381-1385, see entire document.	11-20
X	ISHIDA et al. Association of the Thymidylate Synthase Gene Polymorphism with its mRNA and Protein Expression and with Prognosis in Gastric Cancer. Anticancer Research. September 2002, Vol. 22, pages 2805-2810, see entire document.	11-20
X	CHEN et al. A novel polymorphis in the thymidylate synthase gene promoter influences plasma folate level and may modify the risk of colorectal cancer in a prospective study. Proceedings of the American Association for Cancer Research. March 2002, Vol. 43, page 659, Abstract #3272.	11-20
X	MARSH et al. They thymidylate Synthase enhancer region polymorphism in colorectal cancer. Proceedings of the American Association for Cancer Research. March 1998, Volume 39, pate 434, Abstract # 2955	11-16
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Y		17-20
A	TSUJI et al. Polymorphism in the Thymidylate Synthase Promoter Enhancer Region is Not an Efficacious Marker for Tumor Sensitivity to 5-Fluorouracil-based Oral Adjuvant Chemotherapy in Colorectal Cancer. Clincial Cancer Research. 01 September 2003, Vol. 9, pages 3700-3704.	11-20
A	MARSH et al. Ethnic Variation in the Thymidylate Synthase Enhancer Region Polymorphism among Caucasian and Asian Populations. Genomics. 1999, Vol. 58, pages 310-312.	1-20

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group 1, claims 1-10, drawn to isolated nucleic acid molecules, probes and kits.

Group 2, claims 11-20, drawn to methods for determining whether an individual has a heightened predisposition to cancer or cardiovascular disease.

There is no special technical feature which joins groups I and II, as the methods of claim 11 do not recite or require the products of claim 1 or invention 1. Even if they were to recite or require the products of the main invention, the main invention does not represent an advance in view of the prior art. Lou *et al.* (GenBank AF279906) teach an isolated nucleic acid comprising SEQ ID NO: 1, wherein G is replaced by C at nucleotide 12 (see nucleotides 132-159 of Lou *et al.*). Furthermore, with regard to claim 3, Dean *et al.* (US6087489) teach a single-stranded nucleic acid probe that hybridizes to the isolated nucleic acid molecule of claim 1. Specifically, SEQ ID NO: 16 taught by Dean *et al.* is a 20mer nucleic acid probe which is complementary to nucleotides 7-26 of instant SEQ ID NO: 1, wherein G is replaced by C at nucleotide 12. PCT Rule 13.2 states "The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes *over the prior art* (emphasis added).". Since the main invention was known at the time of filing, there is a lack of unity of invention between group 1 and group 2.